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PATHOLOGY OF LASSA VIRUS INFECTION IN THE RHESUS MONKEY*

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Abstract. The clinical signs and gross and microscopic lesions of Lassa virus infection in the rhesus monkey are described. Of 17 monkeys infected with Lassa virus, nine died or were killed when moribund. The clinical signs were lethargy, aphagia, constipation, fever, conjunctivitis, and skin rash. Pulmonary congestion, pleural effusion, pericardial edema, hydropericardium, and a few visceral hemorrhages were present grossly. Major microscopic lesions were necrotizing hepatitis and interstitial pneumonia. Other microscopic changes were present in the heart, small intestine, spleen, lymph nodes, kidney, urinary bladder, adrenal glands, and central nervous system; however, most of these lesions were mild. In fact, death could not always be attributed to the morphologic changes; therefore, function alterations must be examined.

Lassa fever¹⁻³ is an infectious, febrile disease of man caused by Lassa virus (LASV), a member of the Arenaviridae family. This disease was first recognized in 1969 after it caused the deaths of two missionary nurses.⁴ Rates of fatal cases in hospitalized patients are high; however, mild and subclinical infections occur frequently.⁵⁻⁷

In humans, the clinical syndrome consists of fever, chills, malaise, and various other signs and symptoms.^{4-6, 8-10} Gross lesions are nonspecific and include generalized congestion, edema, and petechiae, especially of the gastrointestinal tract.^{4, 11, 12} Microscopic lesions have been described by a number of investigators.^{4, 11-13} The most consistent and prominent lesion is multifocal hepatic necrosis. Pulmonary edema or interstitial pneumonia have been described. Intestinal lesions include submucosal edema with scattered mono-

nuclear cell infiltrates and mucosal hemorrhages. Other lesions mentioned are lymphoid depletion and degeneration, congestion and slight edema of the heart, and occasional focal tubular and/or glomerular necrosis.

Experimentally, squirrel monkeys (*Saimiri sciureus*),^{14, 15} guinea pigs (*Cavia porcellus*), and rodents (*Mastomys natalensis*) have been infected with LASV.¹⁵ Monkeys had viremia and viral titers above serum levels in lymphoreticular organs, liver, kidneys, and adrenal glands. No significant gross lesions were observed, and microscopic lesions varied. These findings included lymph node changes, myocarditis, arteritis, renal tubular necrosis, nonsuppurative meningoencephalitis, and insignificant hepatic lesions. The disease in the guinea pig was characterized by undefined respiratory insufficiency, a high mortality rate (67%), and lesions compatible with interstitial pneumonia.¹⁵ Laboratory-reared adult *Mastomys* consistently had meningoencephalitis. The wild-caught ones infected with LASV were smaller and had a higher prevalence myocarditis and changes in lymphoid tissue than those without LASV.¹⁶

The purpose of this paper is to describe the gross and microscopic lesions in rhesus monkeys (*Macaca mulatta*) experimentally infected with LASV and compare them with those associated with Lassa fever in humans.

MATERIALS AND METHODS

Lassa virus, Josiah strain, was isolated in 1976 from the serum of a 40-year-old man in Sierra

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Leone.¹⁷ This isolate was passaged four times in an African green monkey kidney cell line (Vero) and stored at -70°C until diluted for use. Infectious LASV was assayed by counting plaque forming units (pfu) on Vero cells maintained as monolayers in 10-cm² wells of plastic plates under agarose, as described previously.¹⁸

Seventeen rhesus monkeys (*M. mulatta*) were injected subcutaneously (sc) with $10^{5.1}$ pfu of the Josiah strain of LASV. All monkeys developed detectable viremia and seroconverted by immunofluorescent antibody test (IFAT) within 10 days of virus inoculation.¹⁸ Necropsy was done on nine monkeys, of which seven died and two were killed when moribund; these constitute the cases reported here. These animals included six monkeys with no detectable preinoculation antibody by IFAT to Lassa, Machupo and Junin virus and three that were negative for LASV antibody which survived previous Junin/Machupo experiments. These Junin/Machupo survivors had neutralizing antibodies to both viruses as determined by plaque reduction neutralization test. At 2- to 3-day intervals, while under ketamine anesthesia, body temperature was taken rectally, and 15 ml of blood was drawn from a femoral vein. Serum was separated, divided into 1-ml aliquots, and stored at -70°C until used. Serum glutamic oxalacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were determined with Worthington Statzyme GOT and GPT kits (Worthington Diagnostics, Freehold, NJ). Preinoculation temperatures averaged 39.1°C , and fever was defined as body temperature above 39.4°C . All work with LASV and infected animals was done in P4 containment.¹⁹

The following tissues were taken from all monkeys for histologic examination: lung, liver, spleen, both kidneys, one adrenal gland, small intestine, heart, pancreas, one submaxillary salivary gland, urinary bladder, lymph nodes (axillary and mesenteric), sex organs and brain. Trachea, esophagus, thyroid, stomach, large intestine, gall bladder, skin, skeletal muscle, spinal cord and spinal ganglia were taken from five to seven of the monkeys.

Tissues were fixed in 10% neutral buffered formalin for a period of 3 weeks with two changes of formalin. Tissues were then processed, sectioned at 6 μm , and stained with hematoxylin and eosin for histopathologic examination. Selected tissues were stained with phosphotungstic acid hematoxylin (PTAH) and for iron (Perls' Method).²⁰

TABLE 1
Serum analysis in four monkeys infected with Lassa virus

Monkey no.	day	Viremia (log ₁₀ pfu/ml)	SGOT* (IU/liter)	SGPT* (IU/liter)
3	3	1.7	31.0	8.0
	5	2.9	38.0	17.0
	7	3.6	48.0	5.0
	10	4.6	139.0	27.0
4	3	2.0	20	18.0
	5	3.2	36.0	15.0
	7	4.1	149.0	33.0
	10	5.5	440.0	152.0
5	3	<0.7	25.0	20.0
	5	3.1	30.0	8.0
	7	4.4	46.0	15.0
	10	6.2	245.0	99.0
6	3	<0.7	20.0	20.0
	5	2.4	27.0	21.0
	7	3.9	61.0	23.0
	10	4.9	1,396.0	437.0

* Preinfection mean values \pm SEM obtained from these same monkeys were SGOT: 29.1 ± 2.06 and SGPT: 17.0 ± 1.93 .

RESULTS

Seventeen rhesus monkeys were infected, and nine died or were killed when moribund. Animals which died usually exhibited lethargy, aphagia, constipation, and fever by day 4. Minimal conjunctivitis and skin rash occurred on or about day 7. This rash consisted of multiple, irregularly shaped, reddish brown macules 1 mm in diameter, which were prominent on the face and eyelids. Body temperature peaked at $40.6-41.1^{\circ}\text{C}$ before declining to subnormal levels prior to death. The mean time-to-death was 11 days with a range of 10-12 days for the arenavirus-negative monkeys and 14.3 days with a range of 12-17 days for the Junin-Machupo survivors.

In comparison, the eight survivors generally developed lethargy and aphagia around day 7 or later, except for one monkey that showed no signs. Survivors demonstrated a similar conjunctivitis and skin rash, while fever developed around day 3 or 4 and was intermittent and variable in duration (4-31 days).

SGOT and SGPT were determined for monkeys 3 through 6 (Table 1). As viremia increased, so did SGOT and SGPT levels.

Gross lesions were variable and generally mild. They consisted of pulmonary congestion, pleural effusion, pericardial edema, hydropericardium,

TABLE 2
Gross necropsy lesions in nine rhesus monkeys infected
with Lassa virus

Gross lesions	No.
Pulmonary congestion	5
Mottled lungs	3
Pulmonary parasitic nodules (2 mm)	3
Pleural fluid	3
Pericardial edema	2
Hydropericardium	2
Hemorrhage	
Endocardium	2
Adrenal gland	3
Urinary bladder mucosa	5
Small intestine	2

and visceral hemorrhages (Table 2). Three monkeys had gross evidence of lung mite infestation. The antemortem skin rash was seldom observed at necropsy, which indicates that it is probably an erythematous phenomenon.

Hepatocellular necrosis (Fig. 1) was a prominent microscopic lesion in all monkeys. It was multifocal, minimal to moderate with mild to moderate mononuclear cell infiltration of portal triads. The necrotic foci were randomly distributed, and varied in size. They consisted of individual to small groups of hepatocytes undergoing coagulative necrosis with sparing of the supporting stroma (Fig. 2). Inflammatory cells infiltrating the necrotic areas generally were few in number, and when present, included neutrophils and mononuclear cells which also were seen in the surrounding sinusoids. Kupfer cells in or near necrotic foci contained cellular debris and occasionally eosinophilic Councilman-like bodies. Most monkeys had a minimal sub-endothelial mononuclear infiltrate in some of the portal and hepatic veins.

Another consistent lesion in all monkeys was interstitial pneumonia. It varied in severity and was characterized by alveolar wall thickening, the result of deposition within septa of eosinophilic proteinaceous material and/or mononuclear cell infiltration. In addition, some septa had cellular

debris, which was suggestive of endothelial cell necrosis, mixed with the infiltrate. Alveolar content varied; in most monkeys, alveoli were mildly infiltrated with macrophages and contained variable amounts of edema fluid and/or fibrin (Fig. 3). A few monkeys had focal alveolar hemorrhage. Multifocal perivascular and occasional sub-endothelial infiltrates of mononuclear inflammatory cells were noted in pulmonary vessels of some animals (Fig. 4). Lung mite lesions were an incidental pulmonary finding in six monkeys.

Heart lesions were present in six of nine monkeys. These consisted of minimal to mild multifocal mononuclear cell infiltrates in the epicardium and myocardium, and occasionally the endocardium. These infiltrates were predominantly lymphocytes with a few plasma cells and macrophages. In addition, the pericardial autonomic ganglia in two monkeys were mildly infiltrated with lymphocytes and plasma cells.

The small intestine had erythrocytes, cellular debris, and macrophages in the lamina propria of villar tips in all monkeys. The macrophages often contained a brown, isotropic pigment which stained positive for iron (hemosiderin). One animal had a severe hemorrhagic infarct of the ileum associated with necrotizing arteritis and multiple venous thrombi of regional mesenteric vessels. Several monkeys also had minimal, perivascular mononuclear cell infiltration in the submucosa.

The spleen in all monkeys had a relative increase in mononuclear cells around the trabecular blood vessels and subendothelially in trabecular veins. Five monkeys had amorphous, eosinophilic material either centrally or peripherally in the Malpighian corpuscles. Lesions in lymph nodes were mild and variable, consisting primarily of lymphocyte depletion and seeming increase in reticuloendothelial cells.

All monkeys had renal lesions. These consisted of multifocal mononuclear cell infiltration around blood vessels at the corticomedullary junction which extended along the interlobular vessels with occasional involvement of the adjacent interstitium. This infiltrate varied in severity from min-

FIGURES 1-4. 1. Liver from a rhesus monkey inoculated with Lassa virus. Multifocal areas of necrosis are scattered throughout the hepatic parenchyma. H & E, $\times 100$. 2. Higher magnification of the hepatic necrosis characterized by cellular debris with minimal inflammatory cell infiltrate. H & E, $\times 200$. 3. Lung with interstitial pneumonia. The alveolar septa are thickened by proteinaceous material and mononuclear cells. Edema fluid and mild infiltrate of macrophages and neutrophils are present in alveolar lumens. H & E, $\times 200$. 4. Pulmonary artery with the endothelium elevated by an intimal infiltrate of mononuclear cells. H & E, $\times 200$.

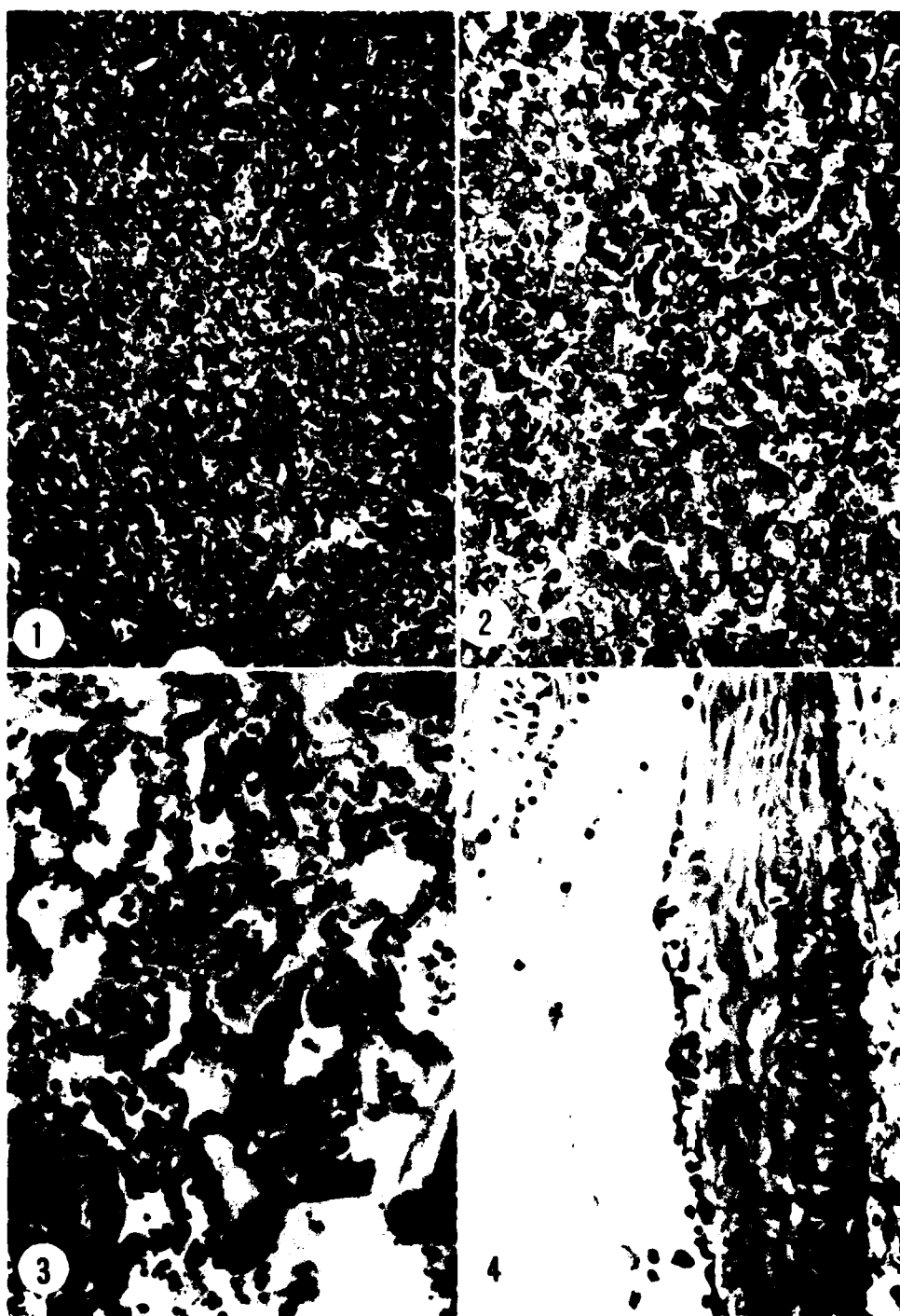




FIGURE 5. Perivascular cuff of lymphocytes in the cerebrum of a Lassa-infected rhesus. H & E, $\times 200$.

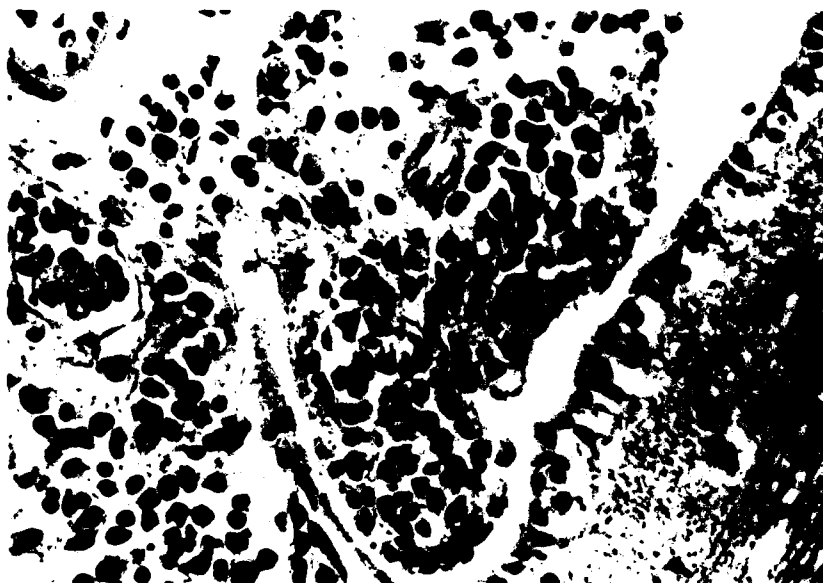


FIGURE 6. Moderate infiltrate of plasma cells and lymphocytes in the choroid plexus. H & E, $\times 400$.

imal to moderate and consisted of lymphocytes with a few plasma cells and macrophages. Two monkeys had a few hyaline and cellular casts in various tubules, while two others had dilated cortical tubules. Thrombosis of an arcuate vein was present in one animal. The pelvis was usually infiltrated with a mild mononuclear cell infiltrate similar to that present perivascularly. A consistent lesion was a mild mononuclear cell infiltrate in the submucosa of the urinary bladder. In addition, three monkeys had submucosal hemorrhages with diapedesis of erythrocytes through the transitional epithelium.

Adrenal cortical infarcts were present in three monkeys in the gland taken for histopathology. In two animals these were of the anemic type and in one the hemorrhagic type. One of these monkeys also had several venous thrombi near the capsular surface. The adrenal glands in the remaining six animals had an occasional necrotic cell in the cortex usually associated with the sinusoids. Two monkeys had a few discrete foci of lymphocytes in the medulla and lower cortex. Five animals had multifocal areas of mineralization at the corticomedullary junction, which is a frequent incidental finding in the rhesus.

Seven of the nine monkeys had lesions in the central nervous system (CNS). These were characterized by mild lymphocytic cuffing of random blood vessels in the brain (Fig. 5), spinal cord and meninges. The choroid plexi of affected animals were always infiltrated with plasma cells and a few lymphocytes (Fig. 6). Spinal ganglia were examined in five monkeys, and in one they were found minimally infiltrated with plasma cells and a few lymphocytes. Only one eye from one monkey was examined; mild choroidoretinitis was present.

DISCUSSION

The clinical disease and lesions in rhesus monkeys resemble those described in man. In this respect, Lassa infection in the rhesus is a more accurate model of the human disease than that produced experimentally in the squirrel monkey^{14, 15} and guinea pig.¹⁵ However, meningoencephalomyelitis, adrenal gland infarcts, and mild arteritis observed in the rhesus have not been described in man. In addition, the deaths of three of seven monkeys previously vaccinated against Junin infection and/or which survived Machupo

infection suggest no cross-protection as measured by survival between Lassa and these arenaviruses.

In a previous paper we reported the virologic and immunofluorescent results of studies on six of the monkeys in this report.¹⁸ Presence of specific immunofluorescence and virus concentrations above serum levels were found in the liver, lung, adrenal gland, pancreas, spleen, kidney, and lymph node. Viral titers were also elevated above serum levels in pleural fluid, but titers were equal to or below serum levels in the brain and spinal cord. Specific immunofluorescence in the CNS was limited to a few cells usually located near blood vessels.

The high virus titers¹⁸ in the liver suggest it is one of the major target organs of virus replication. Although the histopathologic changes in the liver were not considered sufficiently severe to cause death, a significant rise in SGOT and SGPT occurred in several monkeys. These hepatic alterations were a consistent finding and similar in morphology to that described in man.^{4, 11-13} The occurrence of random foci of necrosis, some without associated inflammatory cells, suggests that the hepatic injury may be due to direct viral damage. As specific immunofluorescence¹⁸ did not always correspond to foci of necrosis, it is possible that functional alterations may have occurred in morphologically normal as well as necrotic areas of the liver.

Hepatocytes have a number of critical functions in protein, carbohydrate, and lipid metabolism. The loss of these functions could explain the death of monkeys with mild lesions. Therefore, the concept of arenavirus impairment of "luxury function"²¹ must be given serious consideration in future studies of LASV pathophysiology. This concept surfaced during studies of neuroblastoma cells infected with lymphocytic choriomeningitis virus, another arenavirus.²¹ These cells survived by maintaining vital processes, but functions not necessary for cell viability were altered.

The interstitial pneumonia in the monkey occurred more consistently than the pulmonary edema or pneumonia described in man.^{4, 11-13} Pulmonary lesions seldom were severe enough to be the primary cause of death. However, the lung is an important target organ, as demonstrated by the high virus titers and the specific immunofluorescence in alveolar septa and alveolar macrophages.¹⁸ The role of these macrophages in the

spread or clearance of LASV is currently unknown. The basic mechanism of pulmonary injury is probably vascular damage and resultant increased capillary permeability. This is supported by evidence of endothelial necrosis in alveolar capillaries, fibrin and edema in alveoli, pulmonary arteritis, and pleural effusion (three monkeys). The arterial lesions are similar to those described in experimental serum sickness in rabbits,²² and may represent immune complex disease which is further suggested by the simultaneous occurrence of infections LASV and LASV antibody in the serum. Pleural effusates had the second highest virus titers, suggesting either local virus replication or some concentrating mechanism.

The significance of the heart lesions is questionable. Similar changes have been observed by us and reported by others in a number of primates with varied backgrounds.^{23, 24}

The mild hemorrhage and hemosiderosis in the villi of the small intestine are nonspecific, as we have observed similar changes in monkeys dying of various causes. The intestinal infarct in one monkey was the result of arteritis and thrombosis in regional mesenteric vessels. As these lesions are rare in the rhesus, we suspect that the vascular damage was probably virus-associated especially with evidence of vascular damage in the lung and adrenal gland. Of interest were the markedly elevated viral titers¹⁸ in the pancreas in the absence of microscopic lesions; the significance of this finding must await additional studies.

Adrenal glands had minimal changes except for the three monkeys with cortical infarcts severe enough to cause adrenal gland failure. Two of these infarcts were the anemic type suggestive of arterial blockage. While LASV was present in all glands in high titers, specific immunofluorescence was limited to the zona glomerulosa and the peripheral zona fasciculata.¹⁸ Although these zones appeared normal by light microscopy, their functional status might have been altered. Functional changes in the zona glomerulosa, which is the site of aldosterone production, could have been responsible for a Na and K imbalance.

Kidney lesions were predominantly associated with blood vessels. This finding, coupled with infrequent immunofluorescence (unpublished data) and low virus titers, suggests that virus replication in the kidney parenchyma was unlikely. A few attempts at virus isolation from urine of dead monkeys have been unsuccessful (unpublished data).

The subendothelial mononuclear cells paving trabecular veins of the spleen were present in the rhesus, and resembled the observations in man^{11, 12} and squirrel monkey.^{14, 15} This change has been noted by us in a variety of infectious diseases in the rhesus. The virus titers in spleen and lymph nodes exceeded serum levels, but were lower than those for most other tissues.¹⁸ The immunofluorescent studies indicated that LASV antigen was present in large cells of the splenic red pulp and in similar cells associated with lymph node sinuses.¹⁸ The cells were most likely macrophages or other members of the reticuloendothelial system.

Central nervous system lesions have not been reported in man,^{4, 11} but were recorded in a squirrel monkey.¹⁴ The CNS lesions in the rhesus apparently caused no clinical signs. The mononuclear cell infiltrate and occasional specific immunofluorescence were oriented around blood vessels.¹⁸ These findings, along with the virus titers equal to or below serum levels, suggest a lack of direct neural involvement.

In summary, the rhesus is an excellent model for the human disease. The clinical signs, gross lesions, and histopathological changes in man and monkey have many similarities. Lesions in the rhesus were associated with two principal changes, tissue necrosis and vascular damage. Although these changes were of sufficient severity to explain the death of some monkeys, they were not sufficient to account for the death of all. The high virus titers in some tissues with no apparent morphological changes suggests that impairment of so called "luxury function"²¹ might well play an important role in pathogenesis. Loss of normal function in vital organs, such as liver, pancreas, and adrenal glands, could account for death in animals without severe lesions.

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